Perfusion Imaging of Tumefactive Demyelinating Lesions Compared to High Grade Gliomas

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Keywords: High grade glioma, Perfusion MRI, Tumefactive demyelinating lesion


Tumefactive demyelinating lesions (TDLs) have been defined as demyelinating lesions >20 mm variably associated with mass effect, perilesional edema, and/or contrast enhancement.1-2 A retrospective study of 168 individuals with biopsy-confirmed central nervous system inflammatory demyelinating disease showed that TDLs present a diagnostic challenge given the broad differential diagnosis suggested by conventional magnetic resonance imaging (MRI) sequences (tumour, abscess, vascular disease) and initial misinterpretation of approximately one-third of biopsy specimens by a referring pathologist.1 High grade gliomas (HGGs) are an especially important diagnostic consideration given the shared features of peripheral enhancement, perilesional edema, and mass effect on conventional MRI.3 Cerebral blood volume calculated from dynamic contrast-enhanced perfusion MRI approximates lesion vascularity and may help differentiate TDLs from neoplastic lesions.4-7

CASE CONTROL STUDY

Following Capital Health Research Ethics Board approval (CDHA-RS/2014-127), we performed a retrospective review of all patients with a TDL or HGG pre-operatively imaged using dynamic contrast-enhanced perfusion MRI as part of clinical care at the Halifax Infirmary between July 2010 and September 2013.

Images were acquired using a 1.5 T MRI system (Signa HDxt 1.5 T, GE Healthcare). All patients had axial T2-weighted imaging, axial fluid attenuated inversion recovery (FLAIR) imaging, axial isotropic diffusion-weighted imaging (DWI), magnetic resonance perfusion axial T2*-weighted imaging echo-planar image sequence, and post-gadolinium T1-weighted imaging. For magnetic resonance perfusion, a total of 40 data sets (axial T2*-weighted imaging echo-planar image sequence with TR 2000, TE 26, flip angle 5, matrix 96x128, Nex 1, FOV 22) were acquired with a time resolution of two seconds during and after injection of 0.1 mmol/kg or 0.2 ml/kg of MultiHance (gadobenate dimeglumine, Bracco Diagnostics) at a rate of five ml/s. Total acquisition time was 80 seconds. Acquisition covered the whole head with 20 slices of five mm thickness and inter-slice spacing of 1.5 mm.

Perfusion maps were calculated from time-intensity curves using the vendor provided software package (Functool v. 5.2.09, GE Healthcare). Cerebral blood volume (CBV) and cerebral blood flow (CBF) maps were quantitatively analyzed by placing the region of interest (5-10 mm²) in areas of maximum CBV or CBF on qualitative analysis. Lesion relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) were calculated as a ratio to contralateral normal appearing white matter (Figure 1).

Perfusion MRI was performed for three individuals with a TDL (two biopsy confirmed, one inferred given clinical response to steroids) and six individuals with a HGG (five World Health Organization (WHO) grade IV astrocytoma, one WHO grade III anaplastic oligodendroglioma). There was no difference in age of presentation for patients with a TDL (40.3, range 31-49 years) or HGG (57.2, range 38-70 years) (t = −2.2, p = 0.06). There were more males than females among both TDL (female: male-1:2) and HGG (female: male-1:5) patients. No individual had a prior history of demyelinating disease. Among patients with a TDL, presenting symptoms were visual field defect (n = 2) and confusion (n = 1). Among patients with a HGG, presenting symptoms were confusion (n = 1), dysphasia (n = 1), headache (n = 1), hemiparesis (n = 1), and seizure (n = 1). One patient with a HGG was asymptomatic with incidental detection.

Conventional MRI revealed that two of three TDLs and three of six HGGs presented as solitary lesions (Figure 2). The T2 diameter was similar between TDLs (47.9 ± 34.6 mm) and HGGs (70.1 ± 30.5 mm) (t = −1.0, p = 0.4). All TDLs demonstrated incomplete ring enhancement. All grade IV astrocytomas demonstrated complete ring enhancement while the grade III anaplastic oligodendroglioma was non-enhancing. Perfusion MRI demonstrated that TDLs had significantly lower rCBV (p < 0.01) and rCBF (p < 0.02) compared to HGGs (Table 1). There was no overlap of rCBV (mean ± standard deviation) between TDLs (1.4 ± 0.38) and HGGs (5.03 ± 1.64) as the maximum rCBV among TDLs was 1.55 and the minimum rCBV among HGGs was 2.82. In addition, there was no overlap of rCBF between TDLs (1.26 ± 0.45) and HGGs (4.72 ± 1.80) as the maximum rCBF among TDLs was 1.74 and the minimum rCBF among HGGs was 2.63.

DISCUSSION

In this study, perfusion MRI rCBV and rCBF was lower among TDLs as compared to HGGs. Glioma grade is known to have a strong positive correlation with perfusion MRI rCBV8 and there is a high probability of a HGG with rCBV ≥1.75.9 In one

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study, perfusion MRI rCBV was helpful in distinguishing non-neoplastic lesions (1.0 ± 0.4) from high-grade neoplasms (4.9 ± 3.1; p < 0.001). Therefore, perfusion MRI may be an important imaging modality in the differentiation of TDLs from HGGs.

Overall, perfusion MRI rCBV is lower among TDLs (0.88 ± 0.46) compared to intracranial neoplasms (6.47 ± 6.52; p < 0.01) including gliomas and lymphoma. In a prior study, consistent with the present study, all TDLs had a rCBV <2.0 in contrast to gliomas which had a rCBV greater than 2.0. Primary cerebral lymphoma rCBV ranged from 1.6 to 2.8, making differentiation of TDLs from lymphoma based on rCBV intangible. In addition, there is no difference in perfusion MRI rCBV between non-neoplastic lesions (1.0 ± 0.4) and low-grade neoplasms (1.5 ± 1.2; p = 0.7). Although low grade glioma and primary cerebral lymphoma have a similar rCBV compared to TDLs, neither low grade glioma nor lymphoma mimic high grade glioma or TDLs on routine MRI. On routine MRI, low grade gliomas are typically non-enhancing while lymphomas...

**Figure 1:** Perfusion MRI rCBV and rCBF were calculated as a ratio of lesion (purple) to contralateral normal appearing white matter (green).

**Figure 2:** MRI T2 FLAIR of all individuals with a TDL (top) or HGG (bottom).
typically demonstrate homogeneous enhancement and restricted diffusion on diffusion-weighted imaging.\textsuperscript{12}

Pattern of contrast enhancement may be another useful tool in identifying a TDL. In this study, all TDLs demonstrated incomplete ring-enhancement while this pattern did not occur among the HGG group. In one study, specificity of open-ring sign in differentiating demyelination from a neoplasm or infection was up to 93.8 (95\% CI 85.6 to 98.0) suggesting that demyelination be a consideration when this sign is present.\textsuperscript{13}

**CONCLUSION**

Low perfusion MRI rCBV and rCBF along with incomplete ring enhancement may facilitate diagnosis of TDLs by increasing suspicion of a demyelinating lesion. Imaging features suggestive of a TDL may increase the index of suspicion for a demyelinating lesion. Conversely, perfusion MRI may help to exclude a TDL in patients with established multiple sclerosis with a new mass lesion. At present, imaging cannot replace biopsy in the diagnosis of TDLs. It remains uncertain whether or not non-invasive imaging will eventually replace biopsy in diagnosis of TDLs.\textsuperscript{14}

**DISCLOSURES**

Natalie Parks and Jai Shankar do not have anything to disclose. Virender Bhan has the following disclosures: Biogen Idec, Consultant/Advisor and Principal Investigator, Honoraria and Research support; Novartis, Consultant/Advisor, Honoraria; Teva, Consultant/Advisor, Honoraria; EMD Serono, Consultant/Advisor, Honoraria; Genzyme, Consultant/Advisor, Honoraria.

**REFERENCES**